Community Pharmacists' Contribution to Medication Reviews for Older Adults : A Systematic Review

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COMMUNITY PHARMACISTS' CONTRIBUTION TO MEDICATION REVIEWS FOR OLDER ADULTS - A SYSTEMATIC REVIEW

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ABSTRACT

Background: Inappropriateness of medicine use among older people is a growing concern as populations are aging. As a solution, collaborative medication reviews have been implemented into various health care systems and settings, also increasingly involving community pharmacists.

Objectives: To identify 1) medication review interventions for older adults that involve community pharmacists and 2) evidence of outcomes of these interventions.

Design: A systematic review was performed. Cinahl, MEDLINE (Ovid), Scopus, International Pharmaceutical Abstracts (IPA) and Cochrane Library were sought for articles published between January 2000 and February 2016. Articles involving community pharmacists in medication reviews for outpatients ≥65 years were included. Evidence on economic, clinical and humanistic outcomes of the interventions was summarized.

Results: Sixteen (16) articles were found considering 12 different medication review interventions of which 6 were compliance and concordance reviews, 4 were clinical medication reviews and 2 were prescription reviews according to Clyne et al. typology. Community pharmacists' contribution to reviewing medications varied from sending the dispensing history to other health care providers to a comprehensive involvement in patient's medication therapy management. The most commonly assessed outcomes of the interventions were medication changes leading to a reduction in actual or potential drug-related problems (DRPs) (n=12) and improved adherence (n=5).

Conclusion: Regardless of the community pharmacists' contributions to interventions, medication review interventions seem to reduce drug-related problems and improve medication adherence. More well-designed, rigorous studies with more sensitive and specific outcomes measures need to be conducted to assess the actual impact of the community pharmacists' contribution to reviewing medications and improving health of older adults.

KEY WORDS

Collaborative medication review, Medication therapy management, Community pharmacist, Aged, Geriatric pharmacotherapy

INTRODUCTION

Inappropriateness of medicine use among older people is a growing concern worldwide as populations are aging. Older people are vulnerable to drug-related problems (DRPs) that can be potentially harmful, such as use of medicines without diagnosis, untreated diagnoses, poorly planned combinations of medications with clinically significant interactions, serotonergic and anticholinergic load, adverse drug reactions, inappropriate duration of medication therapy and poor adherence (1). Strategies to solve these problems or even prospectively prevent them to occur has actively been sought (2,3).

As drug-related problems seem to be often linked to poor coordination of care of individual patients, leading to the situation that no one in the care team has overall responsibility of the entire medication or no one regularly reviews the medication, medication reviews have become an important intervention to assure appropriateness of medications of individual patients. Medication reviews, generally carried out by physicians, increasingly involve also pharmacists and nurses (4). These collaborative interventions are frequently performed in various settings, such as hospitals, nursing homes and primary care, but evidence of their effectiveness is still scarce (5). Community pharmacists are also more and more involved in patient care and contribute to reviewing patients' medications. They have potential for active involvement because they meet with older residents regularly while dispensing and may know their everyday health concerns. The aim of this systematic review was to identify 1) medication review interventions targeted at older adults (≥65 years) that involve community pharmacists and 2) to describe the outcomes of these interventions.

METHODS

Search Strategy

A literature search was conducted in December 2014 and updated in February 2016 with the help of an information specialist on Cinahl, MEDLINE (Ovid), Scopus, International Pharmaceutical Abstracts (IPA) and Cochrane Library. Articles published within the period January 2000-February 2016 were included in the study. The search terms covered the following themes: interprofessional, collaboration and use of medicines / medication reviews. The Medical Subject Headings (MeSH) and other terms were used (see an example of the search strategy in Supplementary Dataset S1). This systematic review was carried out by following the Cochrane Collaboration guidelines where applicable (6). The PRISMA checklist was utilized throughout the study (7).

Inclusion and Exclusion Criteria

Original studies and systematic reviews on collaborative medication review interventions for older adults were included if they involved outpatients ≥65 years, community pharmacists contributed to medication reviews, and studies were carried out in developed countries (8). The medication review interventions with only consultant pharmacists were excluded because the interest was in community pharmacists' involvement in medication reviews. No limits were set for research methods nor outcome measures. No control group was required. Articles written in English, Finnish and Swedish were included.

Study selection

The search produced 4265 potentially relevant articles (Supplementary Figure S1). The search focused on all collaborative medication review interventions in different health care settings of which 16 dealt with community pharmacists' contribution to medication review interventions (19-24). Two researchers (SK, AK) independently selected the studies based on titles and abstracts and reviewed the full texts of potential articles for final inclusion. All disagreements were resolved through discussion and consensus with the help of the third researcher (MPM) when necessary.

Data extraction and analysis

Data were extracted using extraction tables (Table 1; Table 2; Supplementary Tables S1-S3) that compiled the following information: medication review intervention and community pharmacists' contribution to it, study design, method for outcome assessment, selected outcome measures applied and the study's outcomes. For assessing the comprehensiveness of each medication review intervention, the Clyne et al. typology was used (25). It classifies medication reviews into three categories according to the purpose of the review: 1) Prescription reviews address technical issues relating to the prescription that can improve the clinical use and cost-effectiveness of medicines and patient safety. It is based on reviewing the medication list and does not require the patient to be present. 2) The compliance and concordance review considers patient's beliefs about medicines and practical barriers for medicine-taking. It usually requires the patient or patient's carer to be present. 3) A clinical medication review is a comprehensive review that takes place with the patient and with access to the patient's notes and laboratory values. It addresses issues relating to the patient's use of medicines in the context of their clinical condition. The medication review process was considered to have the following steps modified from Hepler & Strand's Pharmaceutical Care model (26): 1) Identification of the patients enrolled in the medication review intervention; 2) patient data collection; 3) interviewing the patient; 4) conducting the medication review; 5) counselling the patient; 6) contacting the GP about the medication changes; and 7) following up on the implementation of medication changes. The community pharmacists' reported contribution to each step in medication review interventions was categorized and analyzed. Evidence of economic, clinical and humanistic outcomes of the interventions were summarized with the help of the ECHO Model (27).

RESULTS

Included studies

Sixteen (16) articles met the inclusion criteria, all published in English. Five of the studies were randomized controlled trials (RCTs) (10,12,13,19,20), one of them being a multicenter study carried out in 7 European countries (10). The reminder of the articles (n=11) reported intervention studies (n=2) (9,24), document analyses (n=4) (17,18,21,22), qualitative interviews (n=2) (15,16), a process description (n=1) (11), and a cohort study (n=1) (23) (Supplementary Table S2). One study combined qualitative interviews and a survey (14). Studies were conducted in 13 countries, most commonly in Australia (n=3) (17,18,21), New Zealand (n=3) (15,16,19) and the Netherlands (n=3) (10,13,14).

Medication review interventions involving community pharmacists

The articles (n=16) considered 12 different medication review interventions involving community pharmacists (Supplementary Table S1). Five of the interventions were discussed in more than one article (10,12,13-19) and one of the studies compared two different medication review interventions in two different articles (13,14). Most commonly the interventions were compliance and concordance reviews (n=6) (9-12,20,23,24), followed by clinical medication reviews (n=4) (15-19,21,22) and prescription reviews (n=2) (13,14). Table 1 summarizes community pharmacists' contributions to medication review interventions which are presented in more detail in the following paragraphs.

Table 1. Community pharmacists' contribution to seven steps of medication review interventions (n=12). Names of the interventions are given as in the articles.

7 STEPS OF MEDICATION REVIEWS: / **Name of the intervention:**			Identification of the patients to medication review intervention	Patient data collection	Interviewing the patient	Conducting the medication review	Counselling the patient	Contacting the GP	Following up the patient
PRESCRIPTION REVIEWS (n=2)	Treatment review (13,14)	Written feedback group	✓	✓		✓		✓	
		Case-conference group	✓	✓		✓		✓	✓
COMPLIANCE AND CONCORDANCE REVIEWS (n=6)	(no specific name) (10,12)		✓	✓	✓	✓	✓	✓	✓
	Preventing Falls through Enhanced Pharmaceutical Care (20)		✓	✓	✓	✓	✓	✓	✓
	AGnES study (23)			✓		✓	✓	✓	
	Pharmaceutical Care Research and Education Project (PREP) (11)		✓	✓	✓	✓	✓	✓	✓
	(no specific name) (9)		✓	✓	✓	✓	✓	✓	
	The Four or More Medicines (FOMM) Support Service (24)		✓	✓	✓	✓	✓	✓	✓
CLINICAL MEDICATION REVIEWS (n=4)	General Practitioner-Pharmacist Collaboration (GPPC) study (15,16,19)			✓	✓	✓	✓	✓	✓
	Home Medicines Review (HMR) (17,18)			✓	✓	✓		✓	
	Home Medicines Review (HMR) (21)			✓					
	Comprehensive Medication Review (CMR) (22)			✓	✓	✓		✓	

Prescription reviews (two interventions, two articles)

Both articles, which considered prescription reviews, were about the same intervention (treatment review) experimented in two variations in the Netherlands (13,14). Community pharmacists contributed to the identification of the patient with potential DRPs by a computerized tool integrated in the dispensing data system within the community pharmacy (13,14). They passed on information on clients with a DRP risk to other health care providers. The difference between the two variations of treatment review was the feedback that was given to GPs either in writing or in case-conferences. In those which had case-conferences between community pharmacists and GPs, the community pharmacists also contributed to follow-ups.

Compliance and concordance reviews (six interventions, seven articles)

Two of the articles considering compliance and concordance reviews were about the same multicentre study with the same intervention (10,12). In five out of the six interventions community pharmacists used their patient records to identify patients with potential DRPs and/or for collecting information on patients' medication use (9-12,20,24). The community pharmacist interviewed the patient in five interventions (9-12,20,24). Following the medication review, the community pharmacist discussed the medication with the patient in all the six interventions (9-12,20,23,24). Community pharmacists also contacted patients' GPs about DRPs when needed in all the interventions (9-12,20,23,24) and they contributed to follow up the patient in four interventions (10-12,20,24).

Clinical medication reviews (four interventions, seven articles)

Seven articles on clinical medication reviews concerned four different interventions (15-19,21,22). Three of the articles related to government funded Home Medicines Reviews (HMR) (28) in Australia and reported studies on two approaches to HMR (17,18,21). In the other HMR intervention, community pharmacists interviewed the patients to obtain a comprehensive medication profile and, after conducting the review, wrote a report on the HMR findings and recommendations to the GP (17,18). In the other HMR intervention, community pharmacists contributed by sending the patients' dispensing history to the pharmacists working in the medical center who reviewed the medications (21).

Three articles considered the same General Practitioner–Pharmacist Collaboration (GPPC) experimental intervention in New Zealand (15,16,19). Community pharmacists contributed comprehensively to every step of the medication review intervention and had access to patients' medical records and laboratory values. Community pharmacists also made recommendations for medication changes to the patients' GPs and followed up with the patients clinically during the study period and updated the care plan when needed.

In the Comprehensive Medication Review (CMR) in Finland identification of patients with potential DRPs was made by GPs (22). After receiving the necessary clinical information from the GP, the community pharmacist interviewed the patient at home, prepared a structured case report for the GP and discussed it jointly in a face-to-face case conference to decide on actions which were then documented on the case report with a follow-up plan.

Outcome measures applied and effectiveness of the medication review interventions

Main outcomes of the studies are summarized in Table 2. Outcome measures applied and findings on the effectiveness of the medication review interventions are detailed in Supplementary Tables S2 and S3. In most of the studies (n=13), outcomes were measured as indirect clinical outcomes (9-14,17-20,22-24**),** the Beer's criteria for potentially inappropriate medications (PIMs) (n=2) (18,23), Morisky's Medication Adherence Scale (n=2) (23,24) and Medication Appropriateness Index (MAI) (n=2) (17,19) being used in more than one study. Quality of life was assessed in four of the studies, mostly by using SF-36 (n=3) (10,12,19) or EQ-5D-5L (n=1) (24). Economic outcomes were reported in seven articles (8,9,12-15,22,23,26), direct costs (n=5) (9,10,12,13,24) and time spent on the intervention (n=4) (10,13,14,21) being the most commonly measured.

Table 2. The outcome measures and the main outcomes of the studies (n=16)

THE OUTCOME MEASURES	THE MAIN OUTCOMES ACCORDING TO SIGNIFICANCE
Clinical outcomes	
RCTs (n=5): Indirect: - Pharmacists' recommendations and their acceptance (n=4) (10,13,19,20) - Medicine use and changes to medications (n=3) (10,12,19) - Sign and symptom control (n=2) (10,12) - Patient knowledge of medicines (n=2) (10,12) - Compliance with dosage regimens (n=2) (10,12) - Problems with medicines (n=1) (12) - MAI (n=1) (19)	RCTs (n=5): **Significant outcomes:** - More medicines started in the control group (19) - More changes to medications in intervention group vs. control group (10, 19) - Intervention patients more compliant compared with the control patients (12) - MAI improved in the intervention group (19) **Significance not reported:** - 44% (17%-72%) of pharmacists' recommendations accepted/partially accepted (10,13,19,20) - More changes to medications in case-conference group vs. written feedback group (13) - Better control of medications in intervention group (10,12) - Intervention patients more compliant compared with the control patients (10) - fewer problems with medicines in intervention group vs. control group (12) - 60,8 % (n=124) of the patients' problems (n=204) identified led to positive outcomes (12)
Other studies (n=11): Direct: - Falls (n=1) (24) - Pain (n=1) (24) Indirect: - Pharmacists' recommendations and their acceptance (n=6) (11,14,17,18,22,24) - DRPs (n=4) (9,11,22,23) - Medicines use (n=2) (9,23) - Adherence (n=3) (9,23,24) - PIMs n=2 (18,23) - MAI (n=1) (17) - DBI (n=1) (18)	Other studies (n=11): **Significant outcomes:** - Less falls (24) - More recommendations identified by the pharmacists themselves (than by computerized screening tool) in case-conference group (14) - DRPs (forgetfulness, DDIs, intermittent drug intake) decreased (23) - The median number of regular prescribed medicines fell from 6 to 5 (9) - Better adherence to medication (24) - Patients with non-adherence fell from 38 % to 14 % (9) - MAI scores lower after the intervention (17) - Reduction in the sum of total of DBI scores for all patients (18) **Significance not reported:** - 613 recommendations; 502 to patients (76 % accepted) and 247 to physicians (72 % accepted) (11) - 55% of pharmacists' recommendations were accepted by physicians (22) - Pharmacists made 142 recommendations to prescribers in 110 patients (24) - 559 DRPs in 145 patients: 40 % of the DPRs were resolved, controlled or improved (11) - 785 potential DRPs (6.5/patient); 51% (n=403), resulted in change of drug therapy (22) - The number of patients with one or more DRPs reduced from 94 % to 58 % (9) - Intervention led to a decrease in the use of PIMs (18,23) - Better compliance (23) **Non-significant outcomes:** - Pain scores increased (24) - More recommendations to the GPs in case-conference group than in written feedback group (14) - Self-reported ADRs decreased (23)
Humanistic outcomes	
RCTs (n=5): - HRQoL (SF-36) (n=3) (10,12,19) - Satisfaction/perceptions (n=2) (10,12)	RCTs (n=5): **Significant outcomes:** - HRQoL: emotional role and social functioning reduced (19) - HRQoL: physical functioning and vitality improved in control group (12) - Intervention group more satisfied with the services than the control group (10) **Significance not reported:** - All patients rated services excellent or good (12) - Pharmacists and GPs had a positive opinion of pharmaceutical care (10,12) - HRQoL declined in intervention group (12) **Non-significant outcomes:** - HRQoL declined in general, non-significant differences between the control and intervention groups (10)
Other studies n=11: - Perceptions/opinions (n=3) (14-16) - Ways to improve treatment review method (14) - HRQoL (EQ-5D-5L) (24)	Other studies (n=11): **Significant outcomes:** -HRQoL improved (24) **Significance not reported:** - Pharmacists concerned that they lacked skills and confidence, not mandated to take this role (15) - GPs attributed different values to patient outcomes vs. use of resources which led to continuum between positive and negative responses (16) -Health care professionals were more positive about the process of the treatment review presented personally (14)
Economic outcomes	
RCTs (n=5): - Cost of medication (n=3) (10,12,13) - Cost of intervention (n=2) (10, 13) - Time (n=2) (10, 13) - Number of patients' contacts with health care professionals (n=2) (10, 12) - Hospitalization (n=2) (10, 12)	RCTs (n=5): **Significant outcomes:** - Pharmacists in case-conference vs. written feedback group spent more time on the intervention (13) **Non-significant outcomes:** - Non-significant differences in total cost for intervention and control groups (10, 12, 13) - Lower costs of prescribed medicines in intervention compared to control (12) - Fewer intervention patients were hospitalized (12)
Other studies (n=11): - Time (n=2) (14,21) - Cost of medication (n=1) (9) - Cost of intervention (n=1) (24) - Cost per QALY (n=1) (24) - The billing of the process made by the GPs as a marker of completion of Home Medicines Review process (n=1) (21)	Other studies (n=11): **Significant outcomes:** - The time to complete the process reduced from median of 56 days to 20 (21) - The average cost of medication for 28 days fell from £51,12 to £44,55 (9) **Significance not reported:** - Pharmacists spent more time on the intervention than GPs did (14) - The case conference group required more time than the written feedback group (14) - The support programme resulted in projected savings of £52 per patient per year (9) - Cost of the intervention was estimated to be £98.72 per participant and the probability of being cost-effective was 13,8% (24) - Cost per quality-adjusted life year estimates ranged from £11 885 to £32 466 depending on the assumptions made (24) - A potential financial saving of AUS$ 17 374 during the post-integration phase (21)

ADR = Adverse drug reaction, DBI = Drug Burden Index, DDI = Drug-drug interaction, DPR = Drug-related problem, GP = General practitioner, HRQoL = Health-related quality of life, MAI = Medication Appropriateness Index, PIM = Potentially inappropriate medication, QALY = Quality Adjusted Life Year, RCT = Randomized controlled trial

Randomized controlled trials (n=5)

Five of the included studies were randomized controlled trials with the follow-up period ranging from 9 to 24 months (10,12,13,19,20). None of the RCTs reported direct clinical outcomes. Indirect clinical outcomes considered the most commonly changes in medications (n=4) (10,13,19,20) and pharmacists' recommendations to GPs (n=4) (10,13,19,20). Regardless of the comprehensiveness of the MRI or the community pharmacists' contribution to it, more changes were implemented to intervention group patients than to controls. When reported, GPs accepted or partially accepted on average 44% of the pharmacists' recommendations (17%-72%) (10,13,19,20). The proportion of actual medication changes was reported in four studies (10,13,19,20). Better compliance and control of medical conditions in the intervention group (n=2/2) (10,12) and significant improvement in MAI in the intervention patients (n=1/1) (19) was reported.

Three RCTs (n=3) reported humanistic outcomes (10,12,19). The quality of life had been assessed by using the SF-36 and it mainly showed a decline in some quality of life dimensions, while only one study reported some improvement (12). Two studies (n=2) measured the opinions of the pharmaceutical care services and both reported mostly positive opinions from all parties involved (i.e., patients, GPs and pharmacists) (10,12).

Economic outcomes were reported in two RCTs (10,12). Bernsten et al. (2001) reported some significant cost savings in some countries (10). Sturgess et al. (2003) reported total costs per patient to be lower in the intervention group (12).

Other studies (n=11)

Eleven of the studies were other than RCTs and considered intervention studies (n=2) (9,24), document analyses (n=4) (17,18,21,22), qualitative interviews (n=2) (15,16), a process description (n=1) (11), a cohort study (n=1) (23) and combination of qualitative interviews and a survey (14). Regardless of the community pharmacists' contribution to medication review interventions or their comprehensiveness, interventions led to a reduction in actual or potential DRPs (n=6/6) (9,11,17,18,22,23), better adherence (n=3/3) (9,23,24) and reduction in the number of medicines in use (n=2/2) (9,23). The only direct clinical outcome measured was the number of falls which was found to be fewer in the study group 6 months after the start of the intervention when the study participants performed as their own controls (24).

Indirect clinical outcomes mostly considered community pharmacists' recommendations to GPs to solve potential DRPs (n=6) (11,14,17,18,22,24). One of these studies compared two different prescription review interventions and reported that community pharmacists with a case-conference with the GP made significantly more recommendations which were better accepted than written recommendations (14).

All the qualitative interview studies (n=3) reported humanistic outcomes described as health care providers' perceptions on interventions (14-16). Both positive and negative perceptions were reported (14,15).

Four studies assessed economic outcomes measured with different approaches (n=4) (9,14,21,24). Regardless of the community pharmacists' contribution to intervention, three of the studies (n=3) suggested that the intervention may have saved costs (9,21,24).

DISCUSSION

This systematic review is the first one to summarize the evidence of the community pharmacists' contribution to medication review interventions for older adults. The interventions varied in their comprehensiveness from prescription reviews to clinical medication reviews. Also the community pharmacists' contribution to interventions varied from sending the dispensing history to other health care providers to accessing patients' medical history, interviewing the patient, conducting the medication review, consulting/case-conferencing the findings with the GP, discussing the findings with the patient and following-up the implementation of the medication changes. Regardless of the community pharmacists' contribution to medication review intervention, some positive outcomes were reported, mainly reduction in DRPs and improved adherence. Direct clinical evidence and evidence of economic outcomes of these interventions was scarce.

The community pharmacists' contribution was most extensive in compliance and concordance reviews. Particularly in compliance and concordance reviews community pharmacists involved patients by interviewing them to identify DRPs and advising them in medicine taking. These findings and contributions indicate that community pharmacists can take more responsibility for patient care than they currently do. Their involvement could be facilitated by improving patient information transfer between community pharmacists and other health care providers, e.g., through electronic health records, if the access was extended to community pharmacists. In many of the reported interventions community pharmacists identified patients with potential DRPs by using medication records and computerized screening tools available in the pharmacy and transferred their findings to other health care providers. If the patient information transfer and communication were more accessible, community pharmacists' ability to identify DRPs could be utilized more. The importance of information transfer, as a facilitator to interprofessional collaboration in medication optimization for the older adults, has been reported also in previous studies (5).

Medication changes leading to a reduction of actual or potential DRPs and improved adherence were the measures that most commonly yielded significant outcomes for medication review interventions. Considerable attention had been paid to pharmacists' recommendations and their acceptance by GPs, as well as on the changes in the number of medicines that patients used. All these are indirect outcomes and unspecific indicators of the quality of medication therapy. The number of medicines in use does not necessarily tell how rational the medication regimen is if there is no measurement taken e.g., for potentially harmful medicines and combinations of medicines, nor untreated conditions (29,30). The quality of life was measured only in few studies and showed conflicting results. This may reflect that the measures used were not specific and sensitive enough to indicate any change in the quality of life of older people with impaired coping skills in everyday life. Hence, for future studies, more sensitive and more specific quality of life measures, that have been validated for older people, should be developed (30).

The extent of the community pharmacist's contributions to medication review interventions, as well as assessment methods and outcomes measures applied, varied between studies. Therefore, it is difficult to estimate how the community pharmacists` contribution influenced the outcomes of the medication reviews. When reported, follow-up periods ranged from two months to two years which made it difficult to compare the studies. Interventions were heterogeneous and not always well-documented in the studies which made it unclear what kind of medication review interventions were actually conducted. This may be due to the fact that most of the studies were primarily targeted at some other objectives than introducing a medication review intervention. Given that the majority of the studies were descriptive and measured indirect clinical outcomes, more well-designed studies

with validated and standardized outcome measures are needed to create more rigorous evidence (30). This may facilitate the development of more effective medication review interventions.

The search strategy of this systematic review was comprehensive and the search covered the major potential scientific databases. In addition, the reference lists of the included articles were reviewed to ensure that all relevant articles were identified. To avoid selection bias two or three researchers were involved in the selection process. Categorization of medication review interventions and community pharmacists' contributions to the interventions were quite often challenging because the articles did not provide detailed and comprehensive information on the medication review interventions applied. The comprehensiveness of the search strategy is also a limitation to the study. The aim of the original search was to find interprofessional medication review interventions without limiting it to community pharmacies. Therefore, the search terms were more general than specific which may have excluded some relevant articles.

This systematic review indicates that community pharmacists could be more involved in health care teams and medication review interventions for older adults. There are some promising models in some countries, particularly in Australia, New Zealand and the Netherlands. The more extensive integration and implementation of these community pharmacy services requires recognition in national policy making.

CONCLUSIONS

Community pharmacists could be more involved in medication review interventions for older adults, their contribution extending from identification of DRPs towards more a holistic contribution to medication therapy management. Regardless of the community pharmacists' contributions to interventions, medication review interventions seem to reduce drug-related problems and improve medication adherence. More well-designed, rigorous studies with more sensitive and specific outcome measures need to be conducted to assess the actual impact of the community pharmacists' contribution to reviewing medications and improving the health of older adults.

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SUPPLEMENTAL FILES

Supplementary Dataset S1: An example of the search strategy (Medline).

Supplementary Figure S1: Flow chart of the article selection process.

Supplementary Table S1: Description of medication review interventions in included articles and community pharmacists' contribution to the interventions.

Supplementary Table S2: Description of the studies in included articles: aims, patients, control, time and outcomes measures.

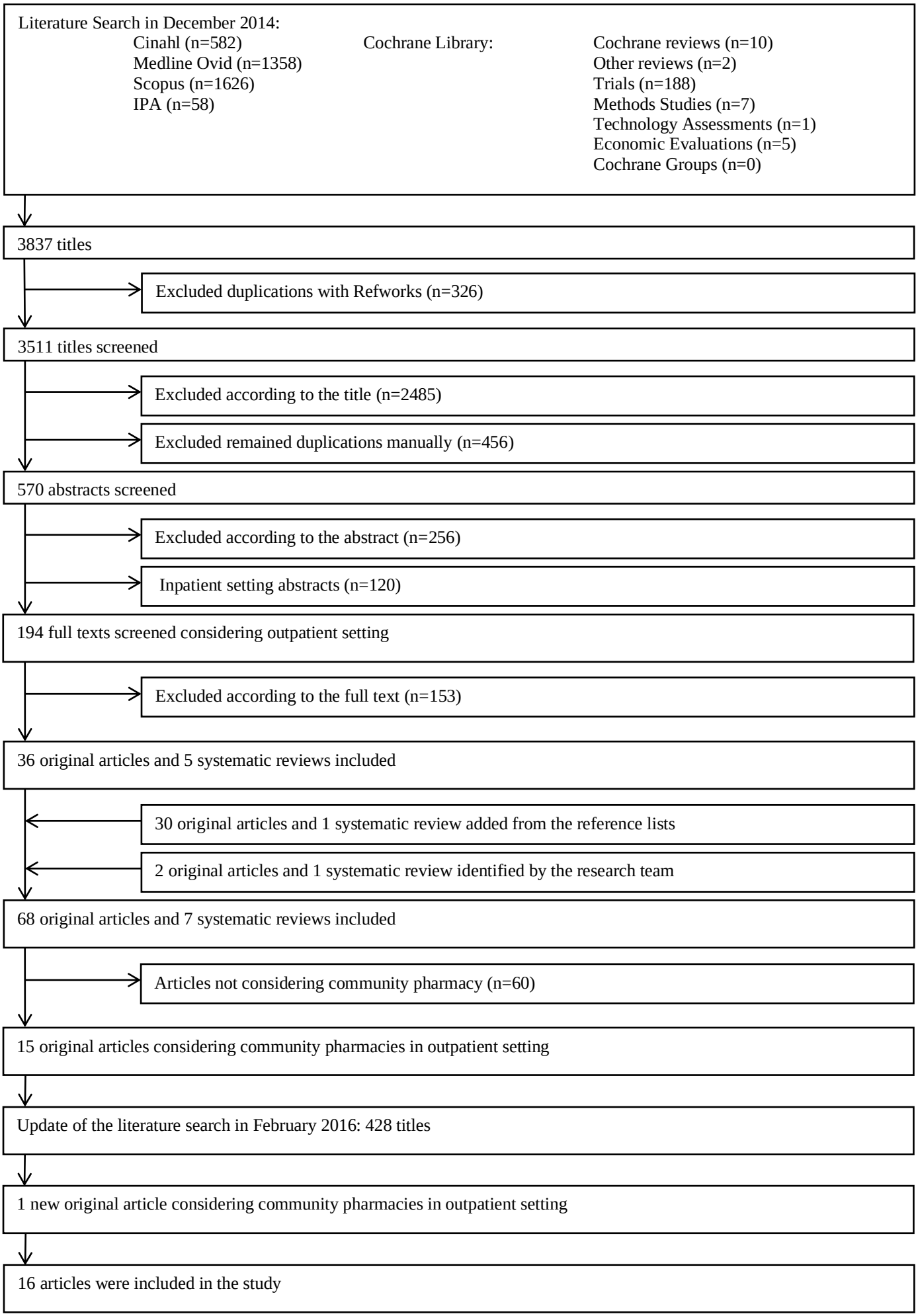
Supplementary Table S3: Outcomes of the studies.

Supplementary Dataset S1

Search strategy for the Medline

1. medication therapy management.mp. or exp Medication Therapy Management/
2. (medicat* adj3 managem*).mp.
3. "medication therapy review".mp.
4. medication reconciliation.mp. or exp Medication Reconciliation/
5. (comprehensive adj3 medicat*).mp.
6. (medicat* adj3 assessment).mp.
7. (medicat* adj3 review).mp.
8. (drug* adj3 review).mp.
9. "clinical pharmacy service".mp.
10. (prescription adj3 review).mp.
11. "clinical interviewing".mp.
12. "medication counseling".mp.
13. (medicat* adj3 harm).mp.
14. (drug* adj3 problem*).mp.
15. polypharmacy.mp. or exp Polypharmacy/
16. (adherence adj3 review).mp.
17. "medication use process".mp.
18. (medicat* adj3 appropriatene*).mp.
19. (medicat* adj3 safet*).mp.
20. inappropriate prescribing.mp. or exp Inappropriate Prescribing/
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 22. interprofessional relation.mp. or exp Interprofessional Relations/
23. inter?professional.mp.
24. multi?professional.mp.
25. multiprofessional.mp.
26. interdisciplinary communication.mp. or exp Interdisciplinary Communication/
27. interdisciplinary health team.mp. or exp Patient Care Team/
28. "medical* care team".mp.
29. team.mp. 62
30. cooperative behavior.mp. or exp Cooperative Behavior/
31. co?operative.mp.

32. cooperative.mp.
33. networking.mp.
34. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 21 and 34
36. 34 and (comprehensive adj3 intervention).mp.
37. 35 or 36
38. ..l/ 37 yr=2000-2014


Literature Search in December 2014:
Cinahl (n=582)
Medline Ovid (n=1358)
Scopus (n=1626)
IPA (n=58)
Cochrane Library:
Cochrane reviews (n=10)
Other reviews (n=2)
Trials (n=188)
Methods Studies (n=7)
Technology Assessments (n=1)
Economic Evaluations (n=5)
Cochrane Groups (n=0)
3837 titles
Excluded duplications with Refworks (n=326)
3511 titles screened
Excluded according to the title (n=2485)
Excluded remained duplications manually (n=456)
570 abstracts screened
Excluded according to the abstract (n=256)
Inpatient setting abstracts (n=120)
194 full texts screened considering outpatient setting
Excluded according to the full text (n=153)
36 original articles and 5 systematic reviews included
30 original articles and 1 systematic review added from the reference lists
2 original articles and 1 systematic review identified by the research team
68 original articles and 7 systematic reviews included
Articles not considering community pharmacy (n=60)
15 original articles considering community pharmacies in outpatient setting
Update of the literature search in February 2016: 428 titles
1 new original article considering community pharmacies in outpatient setting
16 articles were included in the study

Supplementary Table S1.
Description of the medication review interventions (n=12) in included articles (n=16) and community pharmacists' contribution to the interventions.

Reference and country **Study design**	**Name of the medication review inter-vention as given in the article**	**Description of the medication review intervention**	**Community pharmacists' contribution to the medication review intervention**						
			Identificati-on of the patients to medication review intervention	**Patient data collection**	**Inter viewing the patient**	**Conducting the medication review**	**Counsel-ling the patient**	**Contacting the GP**	**Following up the patient**
I Prescription reviews (2 interventions)									
Denneboom et al. 2007 (13) The Netherlands a clustered RCT	A treatment review	1) Patients (≥75 years, ≥5 medicines) were selected from the community pharmacies database. 2) The pharmacist received a list of potential problems identified by the computerized screening tool 3a) The pharmacist listed all recommendations and delivered the written feedback to the GP and did not follow up cases. OR 3b) The pharmacist and the GP discussed all recommendations with each other and filled in a standardized pharmaceutical care plan. The follow-up by the pharmacist in three months.	From the database in pharmacies with the help of a computeri-zed screening-tool	From the database on pharmacies.	-	Deciding which of the recommen-dations highlighted by the screening tool should be given to the GP, and whether additional recommen-dations concerning pharmaco-therapy of the patients should be highlighted.	-	a) Written feedback	-
								b) A case-conference	In 3 months for case conference group.
Denneboom et al. 2008 (14) Netherlands	A treatment review	(see above)	see above	see above	-	see above	-	see above	see above

Question-naire, interviews									
II Compliance and concordance reviews (6 interventions)									
Bernsten et al. 2001(10) Denmark, Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland and Sweden RCT	(no specific name)	Community pharmacists assessed and identified patients individually with actual and potential DRPs using structured approach. Pharmacy interventions included: 1) educating the patient about their drug regimen and medical condition 2) implementing compliance-improving strategies (e.g. drug reminder charts) 3) rationalizing and simplifying drug regimens in collaboration with the patient's GP.	Personal approach by the pharmacist by questioning, from the GP or from the records within the pharmacy	By using number of data sources: the patient by a structured approach, the GP, the records within the pharmacy	During the assessment.	Identifying actual and potential DRPs using a structured approach. An intervention and monitoring plan for the patient.	Educating the patient about their drug regimen and medical condition, implement-ting compliance-improving strategies	Rationali-zing drug regimens together with the GP	6 monthly
Sturgess et al. 2003 (12) Northern Ireland RCT	(no specific name)	1) Identification of patients (community dwelling, ≥4 prescribed medicines, regular visits to pharmacy) via computerized patient medication records kept within the pharmacy. 2) The pharmacist collected data to identify actual and potential DRPs. 3) During the assessment, the pharmacist formulated an intervention and monitoring plan for the patients and visited them at home to assess storage	Via computeri-zed patient medication records kept within the pharmacy	From the patient via questioning, the patient's GP, medical records.	Informal questioning as part of the assessment.	Identifying actual and potential DRPs using a structured approach. An intervention and monitoring plan for the patient.	An intervention and monitoring plan for the patients and visiting them at home to assess storage of medicines where problems identified.	Patients were referred to their GP or the GPs were contacted personally to discuss the problem.	6 monthly (by e.g. pharmacist assistant)

		of medicines where problems were identified.							
Casteel et al. 2011 (20) USA RCT	Preventing Falls through Enhanced Pharmaceuti-cal Care	Medication consultation: the community-based pharmacy resident reviewed the patient's medication with the special attention on medications reported to increase the risk for falls. Resident faxed a note in the SOAP (Subjective information, objective information, assessment, and plan) to the prescribing provider. The prescriber informed the resident of the medication changes and the resident contacted the patient by telephone.	From the prescription records of community pharmacies.	From the prescription records and a telephone interview.	When collecting the baseline data.	Identifying potential DRPs and a risk for falls during the medication consultation.	Medication consultation	Faxing the note in the standard SOAP format to the prescribing provider	Following the patient by telephone and assisting with the implemen-tation of any authorized medication changes.
Fiß et al. 2013 (23) Germany A prospective non-randomized implementati-on cohort study	AGnES (GP-supporting, community-based, e-health-assisted systematic intervention) -study	1) The GP decided which patients needed home visits. Inclusion criteria was any intake of medicines. 2) Nurses interviewed patients at their home and had a home medication review. Standard interview detected adherence problems, ADRs during the last four weeks, the use of adherence supporting activities and record of all medicines (prescribed and over-the-counter) 3) Pharmaceutical care by community pharmacist: the pharmacist received the report of patient's medication and analyzed it. 4) The pharmacist provided	-	-	-	Conducting pharma-ceutical care based on a standardi-zed report from a home medication review.	Usually providing specific advice to the patient about correct drug usage.	If necessary, recommenda tions to the GP for modificati-on of pharmaco-therapy.	-

		advice to the patient about the correct medicine usage and gave recommendations to the GP if necessary. 5) A follow-up visit (not reported by whom)							
Kassam et al. 2001(11) Canada A process description	Pharma-ceutical Care Research and Education Project (PREP)	The community pharmacist telephone interviewed the patients (≥65 years of age, ≥3 medicines according to pharmacy dispensing records). The pharmacist used PMDRP (Pharmacists' Management of Drug-Related Problems) form and SOAP (Subjective information, objective information, assessment, and plan) notes to document care. The pharmacist made recommendations to physicians.	Pharmacy dispensing records.	Using the PMDRP form during the interview.	Telephone interviews.	Identificati-on of DRPs based on the PMDRP form and they were ranked according to importance. Interventi-ons were documented using SOAP notes.	Recommen-dations and counselling for the patients	Recommen-dations for patients' GP	Follow-up plan written in the SOAP notes, Following the patients by contacting them.
Raynor et al. 2000 (9) UK Intervention study	(no specific name)	1) Local general practice surgery computer identified patients ≥65 years 2) The pharmacy patient medication records system identified patients with ≥4 regular medicines. 3) Pharmacy and surgery staff identified the patients living alone by their personal knowledge. 4) The pharmacist conducted structured assessment interview at the patients' home: the reviewing of patients' medicines, issues relating to adherence and DRPs.	First from the local general practice surgery computer (for the right age), then from the pharmacy patient medication records (for the number of medicines) and then from the personal knowledge	From the patient.	At the patient's home using a structured assessment interview. (The assessment visit).	Identificati-on of DRPs and adherence issues, following a discussion with the patient and writing an action plan. Implemen-tation of necessary changes to the patient's medication	The second home visit: discussion with the patient of medication regimen and possible changes made.	Liasing with the GP about implementati on of medication changes in relevant cases.	-

		5) The pharmacist drew up an action plan. Liasing with the GP and other carers. 6) The pharmacist made a second home visit with a new supply of medicines, discussed the medication regimen with the patient and explained any changes that had been made.	of pharmacy and surgery staff (for living alone or not)						
Twigg et al. 2015 (24) UK Intervention study	The four or more medicines (FOMM) support service	1) Pharmacy or another health care professional (e.g. GP) invited the patient to the service. 2) Pharmacist used patient medication records and a subset of STOPP/START criteria. These criteria were listed on the patient's personal service record. If particular criterion was present, then the pharmacist ticked the box, and this prompted them to make a recommendation to the GP 3) Pharmacist discussed the assessment with the patient and asked specific questions relating to fall risk, pain management and adherence, where appropriate. The pharmacist made recommendations to the patient and referred to the GP when necessary. 4) The pharmacist discussed the STOPP/START assessment with the patient's GP if necessary.	In pharmacy by telling about the service or from other health care profession-nals who had told patients about the service.	From the pharmacy medication record.	Discussing the assessment with the patient and asking specific questions.	Using pharmacy medication record and a sub-set of STOPP/ START criteria.	Making recommenda tions to the patient if necessary.	Making recommenda tions to the GP if necessary.	On a regular basis depending on when the patient collects repeat medication or feel a need.

		5) Patients met with the pharmacist on a regular basis depending on when they collected their medications or they felt a need.							
III Clinical medication review (4 interventions)									
Bryant et al. 2011 (19) New Zealand RCT	General Practitioner - Pharmacist Collaboration (GPPC) study	1) GPs invited the patients. 2) Gathering of patient information (pharmacist had access to patients' medical records information including problem list, medication and laboratory values) 2) Medication review in pharmacy or at patient's home. The use of standardized comprehensive data-collection forms. Recommendations to the prescriber and patient. 3) Follow-up consultation with the patient.	-	Gathering of patient information (pharmacist had access to patients' medical records information including problem list, medication and laboratory values)	In pharmacy or at patient's home.	Assessment of the medicines including identifying of drug therapy problems. Preparing a care plan.	Consultati-on with the patient.	Recommen-dations to the GP in a meeting after the patient consultati-on.	Follow-up consultati-on with the patient at 3, 6 and 12 months and updating the pharma-ceutical care plan when needed.
Bryant et al. 2010a (15) New Zealand Interview	General Practitioner - Pharmacist Collaboration (GPPC) study	Pharmacist met with the patient (>65 years of age, ≥5 medicines) with access to patient medical records, and then met the GP to discuss potential medication alterations.	-	see above	see above	see above	see above	see above	see above

Bryant et al. 2010b (16) New Zealand Interview	General Practitioner - Pharmacist Collaboration (GPPC) study	Pharmacist met with the patient (>65 years of age, ≥5 medicines) with access to patient medical records, and then met the GP to discuss potential medication alterations. The patient was met in pharmacy or at home. A meeting with the GP.	-	see above	see above	see above	see above	see above	see above
Castelino et al. 2010a (17) Australia A retrospective analysis	Home Medicines Review (HMR)	1) The GP referred the patient to the patient's preferred pharmacy based on standard criteria (≥5 medicines or a medicine with narrow therapeutic index). 2) Pharmacist interviewed the patient usually in the patient's home to obtain a comprehensive medication profile. 3) the pharmacist wrote a report on HMR findings and recommendations to the GP. 4) The GP and the patient agreed on a medication management plan based on the HMR report.	-	From the patient's interview	Usually in the patient's home	After the interview pharmacist prepares a written report document.	-	A written report document.	-
Castelino et al. 2010b (18) Australia A retro-spective analysis	Home Medicines Review (HMR)	(see above)	-	see above	see above	see above	-	see above	-
Freeman et al. 2012 (21)	Home Medicines	In the medical center, the GP or the community nurse identified	-	Community pharmacies	-	-	-	-	-

Australia A retro spective analysis of medication reviews with two time periods	Review (HMR)	the patient for a HMR. The GP signed the referral and gave it to practice pharmacist who sent a copy to patients' community pharmacy. The community pharmacy sent copy of the patients' dispensing history and any other relevant information. The practice pharmacist interviewed the patient in the medical center or at the patient's home to identify DRPs. The HMR report was uploaded into the medical software with an alert sent to the GP and the copy was sent to the community pharmacy. The practice pharmacist discussed the medication review with the GP. The patient was called for an appointment with the GP and may be referred for another HMR later if the GP considers it necessary		received a copy of the HMR referral from practice pharmacist and sent back a copy of the patient's dispensing history.					
Leikola et al. 2012 (22) Finland A retro-spective analysis	Comprehen-sive Medication Review (CMR)	1) The GP selected the patients based on potential problems or risks in the patients' pharmacotherapy. 2) The patients were asked for a written consent. 3) The GP provided patients' clinical information to the community pharmacist. 4) The pharmacist interviewed the patients at patients' homes using a structured interview form.	-	From the patient's GP	At the patient's home using a structured interview form.	Detecting DRPs based on clinical information and the interview. Preparing a structured case report.	-	A structured case report with findings and recommen-dations to the GP. A face-to-face case conference to determine actions. Documenta-tion of decisions to the case report.	-

		5) The pharmacist prepared structured case reports for each patient with findings and recommendations for the GP. 6) The pharmacist and the GP (and a nurse) had a face-to-face case conference to determine actions. The decisions were documented on the case report.							

DRP = Drug-related problem
GP = General practitioner
RCT = Randomized controlled trial
STOPP = Screening Tool of Older Person's Prescriptions
START = Screening Tool to Alert doctors to Right Treatment

Supplementary Table S2. Description of studies (n=16).

Reference	Aim of the study	Patients	Control	Time	Outcome measures
Bernsten et al. 2001 (10) RCT Denmark, Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland and Sweden	To measure the outcomes of a harmonized, structured pharmaceutical care programme provided to patients (≥65 years of age, ≥4 prescribed medicines) by community pharmacist in a multicentre international study performed in 7 European countries	Community dwelling, ≥65 years of age, ≥4 prescribed medicines. Patients were required to orientate with respect to self, time and place. Regular visits to community pharmacy. n = 1290 from 104 pharmacies received structured pharmaceutical care programme.	Community dwelling, ≥65 years of age, ≥4 medicines. Regular visits to community pharmacy. n = 1164 from 86 pharmacies received normal services.	18 months (0,6,12, and 18)	<u>Clinical:</u> Indirect: -sign and symptom control -Medicines use -Number of times medication regimens were changed -GPs' acceptance of recommendations -Patient knowledge of medicines -Compliance with dosage regimens (questionnaires developed by the research group)
					<u>Humanistic:</u> -HRQoL (SF-36) -Patient satisfaction with the services (a questionnaire) -The pharmacists' and GPs' satisfaction (a questionnaire)
					<u>Economic:</u> The total cost of intervention divided into: - additional time spent by pharmacists - patients contacts with GPs, specialists and nurses - number of hospital admissions (self-reported by the pharmacists and the patients) - cost of drugs prescribed (from pharmacy records)
Bryant et al. 2011 (19) RCT	To determine whether the involvement of community pharmacists undertaking medication reviews, working	≥65 years of age, ≥5 prescribed medicines received Comprehensive	65 years of age, ≥5 prescribed medicines received usual care n = 229	12 months: Intervention group: 0,3, 6 and 12 months).	<u>Clinical:</u> Indirect: - MAI - change in the numbers of medicines used

New Zealand	with GPs, improved medicine-related therapeutic outcomes for patients.	Pharmaceutical Care (CPC) n = 269		The control group received the intervention at 6 months and were followed at 0,3, and 6 months.	- the number of changes to medicines therapy - number of recommendations made and implemented <u>Humanistic:</u> - QoL (SF-36) <u>Economic:-</u>
Casteel et al. 2011 (20) RCT USA	To report on retrospective process evaluation of data from a RCT conducted to examine the effectiveness of a medication review intervention, delivered through community pharmacies, on the rate of falls among community-dwelling older adults.	≥65 years of age, ≥4 prescription medicines filled in the previous 12 weeks and had prescription filled for ≥1 high-risk medication. + having fallen in the last 12 months, living at home, able to come to a pharmacy, knowing English language, <3 errors on the Mini-Mental State Examination. Received medication consultation. n=93	≥65 years of age, ≥4 medicines filled in the previous 12 weeks and had prescription filled for ≥1 high-risk medication. + having fallen in the last 12 months, living at home, able to come to a pharmacy, knowing English language, <3 errors on the Mini-Mental State Examination. n=93	24 months: prescriptions filled 12 before randomizations continuing 12 months after randomization	<u>Clinical:</u> Indirect: - whether the prescriber authorized the recommendations made by the pharmacy resident - whether the recommendations were implemented or not implemented - the number of recommendations made by pharmacy residents - whether the prescriber responded to the note <u>Humanistic:-</u> <u>Economic:-</u>
Denneboom et al. 2007 (13) a clustered RCT Netherlands	To compare two different procedures for treatment reviews (case conferences and written feedback) and the number of medication changes in them. To determine the costs and savings related to the intervention.	home-dwelling ≥75 years of age, ≥5 prescription medicines continuously. Two intervention groups: 1) a written-feedback group: 351 patients in 13 pharmacies 2) a case-conference group: 387 patients in 15 pharmacies	The two intervention groups were each other's controls	9 months: (0,6 and 9)	<u>Clinical:</u> Indirect: - the number of clinically-relevant recommendations (clinical relevance identified by earlier analysis, literature or an expert panel) - the number of medication changes following the recommendations - whether the medication changes had been maintained - clinical relevance of the recommendations leading to medication changes <u>Humanistic:</u>-

					Economic: - Changes in costs of medicines used - Costs of the treatment reviews - Time consumed by the intervention
Sturgess et al. 2003 (12) RCT Northern Ireland	To measure the outcomes of a harmonized, structured pharmaceutical care programme provided to elderly patients by community pharmacists.	Elderly, ambulatory, community dwelling patients 65 years of age, ≥4 prescribed medicines, regular visits to community pharmacy received pharmaceutical care intervention. Patients were required to orientate with respect to self, time and place. (n=110)	Elderly, ambulatory, community dwelling patients 65 years of age, ≥4 prescribed medicines, regular visits to community pharmacy received normal services. Patients were required to orientate with respect to self, time and place. (n=81)	18 months (0,6,12 and18 months)	Clinical: Indirect: - Medicines use - Number of changes in medicines - Problems with medicines - Sign and symptom control - Patient knowledge of medicines - Compliance with dosage regimens (questionnaires developed by the research group)
					Humanistic: - HRQoL (SF-36) - Patient satisfaction with the services provided (a questionnaire) - Pharmacists' perceptions of the study and pharmaceutical care (a questionnaire)
					Economic: - Costs - Number of hospitalisations - Medicines use - Number of patients' contacts with health care professionals
Bryant et al. 2010a (15) Interview New Zealand	To explore possible attitudinal factors that prevent increased participation of community pharmacists in medication reviews undertaken in collaboration with GPs.	Pharmacists who had started the General Practitioner-Pharmacist Collaboration (GPPC) study (n=20).	-	Interviews were undertaken at the end of the GPPC study.	Clinical:
					Humanistic: - Community pharmacists' perceptions of clinical medication reviews
					Economic:-
Bryant et al. 2010b (16) Interview New Zealand	To explore the perceptions of GPs to determine possible barriers that limit community pharmacists and GPs working together clinically.	GPs who had started the General Practitioner-Pharmacist Collaboration (GPPC) study (n=38).	-	Interviews were undertaken at the end of the GPPC study.	Clinical:-
					Humanistic: - GPs' perceptions of clinical medication reviews undertaken by community pharmacists.
					Economic:-

Castelino et al. 2010a (17) A retro-spective analysis Australia	To retrospectively evaluate the impact of Home Medicines Reviews (HMRs) on the appropriateness of prescribing.	Community-dwelling older people (≥65 years, on the basis of standard criteria, e.g. ≥5 medicines or medicine with narrow therapeutic index) (n=270)	-	Retrospectively from HMRs conducted between February 2006 and October 2009.	<u>Clinical:</u> Indirect: - MAI scores at baseline and after the HMR service as a tool to categorize pharmacists' recommendations <u>Humanistic:</u>- <u>Economic:</u>-
Castelino et al. 2010b (18) A retro-spective analysis Australia	To investigate whether Home Medicines Review (HMR) services would lead to an improvement in the use of medicines.	Community-dwelling older people (≥65 years, on the basis of standard criteria, e.g. ≥5 medicines or medicine with narrow therapeutic index) (n=372)		Retrospectively from HMRs conducted by community pharmacists	<u>Clinical:</u> Indirect: - The total Drug Burden Index (DBI) score at baseline and post-HMR - The extent of PIM use (2003 Beers' criteria) - Number and nature of pharmacists' recommendations <u>Humanistic</u>:- <u>Economic:</u>-
Denneboom et al. 2008 (14) Question-naire, interviews Netherlands	To describe the feasibility of two methods for treatment review (case conferences and written feedback)	Patients ≥75 years of age, ≥5 medicines. Two intervention groups: 1) a written-feedback group: - 351 patients - 13 pharmacists of whom 9 randomly selected were telephone interviewed - 8 randomly selected	-	Written questionnaires were sent after treatment reviews. Reminders of questionnaires after 2 and 5 months. Interviews were conducted after	<u>Clinical</u>: Indirect: - the number of recommendations for each patient - the number of clinically relevant recommendations (clinical relevance identified by earlier analysis, literature or an expert panel) - origin of the recommendations (pharmacist/computerized screening tool) <u>Humanistic:</u> - GPs and pharmacists' opinions of the treatment review - ways to improve treatment review method

		GPs were telephone interviewed 2) a case-conference group: - 387 patients - 15 pharmacists of whom 9 randomly selected were telephone interviewed - 8 randomly selected GPs were telephone interviewed		treatment reviews.	Economic: - time spent in performing treatment reviews
Fiß et al. 2013 (23) A pro-spective non-randomized implementa-tion cohort study. Germany	To reduce several DRPs by the implementation of a three party health care team and adherence supporting strategies	Home-dwelling elderly in German rural areas (n=408)	-	Study period 06/2006-12/2008. Mean participation time 9 months.	Clinical: Indirect - self-reported DRPs (Morisky Scale; study specific questions) - objectively evaluated DRPs (PI-Doc system; ABDA Database) - PIMs (Beer's criteria) - Medicines use (active substances identified by using ATC-codes) - prevalence of adherence supporting strategies (study specific questions)
					Humanistic:-
					Economic:
Freeman et al. 2012 (21) A retro-spective analysis of medication reviews with two time periods Australia	To describe the effect of integrating a pharmacist into the GP team on the timeliness and completion of pharmacist-conducted medication reviews compared with referral for Home Medicines Review (HMR) to a community pharmacist	Patients who had received referral for HMR according to medical centre database. Pre-integration of practice pharmacist (n=70) and post-integration of practice pharmacist (n=314).	-	Two time periods were analysed: Pre-integration of practice pharmacist from October 2001 to March 2009 (90 months) and post-integration of practice pharmacist from	Clinical: -
					Humanistic:
					Economic: - the billing of the process made by the GPs as a marker of completion of HMR process - the median number of days between HMR referral and the pharmacist consultation with the patient with the median number of days between HMR referral

				April 2009 to May 2010 (12 months).	and the GP follow-up consultation with the patient (the entire medication review process) - the proportion of patients seen by the pharmacist and the GP at follow-up at 2 and 4 weeks
Kassam et al. 2001 (11) Descriptive analysis of the treatment group from a larger randomized, controlled cluster design. Canada	To describe the process of care used by community pharmacists participating in the Pharmaceutical Care Research and Education Project (PREP).	Patients ≥65 years of age, ≥3 concurrently used medicines according to pharmacy records in intervention pharmacies. n=159	-	15 months	<u>Clinical:</u> Indirect: - frequency of DRPs by using the Pharmacists' Management of Drug-Related Problems (PMDRP) form - status of DRPs analysis of clinical results as determined during pharmacists' follow-up care - recommendations
					<u>Humanistic:</u>
					<u>Economic:</u> -
Leikola et al. 2012 (22) Retro-spective analysis Finland	To assess DPRs documented by specially trained community pharmacists during the Finnish comprehensive medication review (CMR) procedure and to describe the resulting interventions for home-dwelling and assisted-living primary care patients ≥65 years	Home-dwelling (n=70) and assisted-living (n=51) primary care patients ≥65 years. Pharmacists (n=26).	-	During the 1,5-year CMR accreditation training in 2006-2007.	<u>Clinical:</u> Indirect: - DRPs (PCNE classification for DRPs) - physicians' acceptance of pharmacists' recommendations
					<u>Humanistic:</u>
					<u>Economic:</u> -
Raynor et al. 2000 (9) Intervention study UK	To devise, implement and evaluate a medication adherence support service by community pharmacists for elderly patients living at home and at risk of non-adherence.	Patients ≥65 years of age, ≥4 regular prescription medicines, living alone (n=143).	-	8 (+/- 1) weeks	<u>Clinical:</u> Indirect: - number of prescribed regular medicines - number and nature of medicine-related problems - self-reported adherence
					<u>Humanistic:</u>
					<u>Economic:</u> - cost of medication
Twigg et al. 2015 (24) Intervention	To describe the effect of a holistic community pharmacy-based service with	≥65 years of age, ≥4 medicines (n=620) in 25 community	-	9/2012-6/2013	<u>Clinical:</u> Direct: - Falls, pain (MMAS-8 score)

study UK	patients over the age of 65 years old and prescribed four or more medicines (FOMM)	pharmacies of whom 441 (71,1 %) completed the 6-month study period.			Indirect: - pharmacists' recommendations - adherence (MMAS-8 score)
					<u>Humanistic:</u> - HRQoL (EQ-5D-5L)
					<u>Economic:</u> - the costs of intervention - cost per QALY

ABDA = German Federation of Pharmacists
ATC codes = Anatomical Therapeutic Chemical classification system
CEAC = Cost-effectiveness acceptability curve
DRP = Drug-related problem
GP = General Practitioner
HRQoL = Health-related quality of life
MAI = Medication Appropriateness Index
MMAS-8 = Morisky Measure of Adherence Scale-8
PCNE = Pharmaceutical Care Network Europe
PIM = Potentially Inappropriate Medications
QALY = Quality-adjusted life year
QoL = Quality of life
RCT = Randomized controlled trial

Supplementary Table S3. Outcomes of the studies (n=16).

Reference	Community pharmacists' contribution to medication review intervention	Outcomes of the studies		
		Clinical outcomes	Humanistic outcomes	Economic outcomes
I Prescription reviews				
RCTs (n=1)				
Denneboom et al. 2007 (13)	• Identification of the patients to medication review intervention • Patient data collection • Conducting the medication review • Contacting the GP • Following up the patient (in a case-conference group)	Indirect: - Pharmacists in the case-conference group identified significantly more recommendations themselves than the pharmacists in the written-feedback group (41,7 % vs. 34,2 %, p = 0.003) - 1569 recommendations were made (62% by the screening tool, 38% by the pharmacists) - more recommendations in case-conference group (p = 0.059) - for clinically-relevant recommendations significantly more medication changes were initiated in the case-conference group (42 vs. 22, p = 0.02) - This was also seen for the percentage of maintained medication changes 6 months after the treatment reviews (36 vs. 19, p = 0.02)		
Other studies (n=1)				
Denneboom et al. 2008 (14) Questionnaire, interviews	• Identification of the patients to medication review intervention • Patient data collection • Conducting the medication review • Contacting the GP • Following up the patient (in a case-conference group)	Indirect: - more recommendations to the GPs in case-conference group (chi-square, p = 0.059) - The number of recommendations with direct clinical relevance per patient is almost equal for both intervention groups	- Health care professionals were more positive about the process of the treatment review presented personally although there were not always as many recommendations as they had hoped for - Both positive and negative factors influenced the results of	-Pharmacists spent more time on the intervention than GPs did. - Health care professionals gave more of their time in the case conference-group than in the written feedback group

		- significantly more recommendations identified by the pharmacists themselves in case-conference group (chi-square, $p = 0.003$) - intervention with personal contact in case-conferences accepted better than an intervention with feedback in writing	the intervention. Cooperation and personal relationship between the pharmacist and the GP were said to be both positive and negative in performing treatment reviews. The time required and specialists' prescriptions were named as negative factors influencing the results of the intervention. - concrete suggestions for improving the intervention such as a combination of case-conferences and written feedback and reserving the case-conferences for the most complex cases	
II Compliance and concordance reviews				
RCTs (n=3)				
Bernsten et al. 2001 (10)	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	Indirect: - The medical conditions were controlled better during the study in intervention group (at 6 months 73 %, at 12 months 71 % and at 18 months 75 % of the patients agreed) - No significant differences between the control and intervention with regard to prescription and nonprescription drug use. - 50 % of GPs considered the recommendations - there were significantly more changes in medication self-reported by the intervention group than by the control group at baseline and the 6-month assessment (Mann-Whitney test, $p < 0.05$) - No significant differences	-HRQoL declined in both groups in general except in some domains in some countries: significant improvements in general health and role emotional scores compared to control patients in Denmark (independent t-test, $p < 0.05$) - In the pooled data, there were no significant differences between the control and intervention patients in any of the 8 dimensions over time (AUC summary measure analysed; independent t-test, $p > 0.05$) - patients in intervention and control groups were satisfied with the services but intervention patients rated the services significantly higher at 6	-No significant differences between the total cost for control and intervention patients in any country (Mann-Whitney, $p > 0.05$) - Some significant differences in individual components (e.g. in Germany intervention patients had significantly lower costs associated with hospitalisations and contact with specialists compared to controls (Mann-Whitney test, $p < 0.05$) - more hospital visits in control group (non-significant) - No significant differences between the control and intervention regard to contact with GPs

		between the control and intervention with regard to knowledge of medicines - at 18 months significantly higher proportion of the intervention patients changed from being noncompliant to compliant compared with the control patients (15,2 % and 12,2 , respectively; Chi-squared, p = 0.028)	and 18 months compared to control patients (Mann-Whitney test, $p < 0.05$) and there were statistically significant increases in satisfaction in the intervention group over time (baseline 92,0 % vs. 6 months 95,1 %, Wilcoxon test, p = 0.012; baseline 92,0 % vs. 12 months 93,9 %, Wilcoxon test, p = 0.039) - 80 % of pharmacists and 52 % of GPs had a positive opinion of pharmaceutical care	
Sturgess et al. 2003 (12)	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	Indirect: - The medical conditions were controlled better during the study in intervention group (proportion of patients who agreed: 6 months 87,8 %, 12 months 85,1 %, 18 months 83,1 %) - fewer problems with their medicines in intervention group compared to control during the last 6 months of the study (Mann-Whitney, $p < 0.05$) - No significant differences in medicines use between intervention and control group - 60,8 % (n=124) of the patients problems (n=204) identified led to positive outcomes - compliance with medication significantly higher in intervention patients compared to control patients (chi-square, $p < 0.05$) - patient knowledge of medicines were comparable in intervention and control groups	--HRQoL declined in intervention group and improved in control group in some of the SF-36 dimensions (physical functioning and vitality, independent t-test, $p < 0.05$) - All patients rated services excellent or good - GPs had positive opinion about service - Pharmacists had a positive opinion on the pharmaceutical care programme	-total costs 131,65£ lower per patients in intervention group than in control group during the intervention (Wilcoxon test, $p > 0.05$) - Intervention patients incurred lower costs associated with their prescribed medicines compared to control patients (Mann-Whitney test, $p > 0.05$) - fewer intervention patients were hospitalized (non-significant) - little impact of health care utilizations

Casteel et al. 2011 (20)	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	Indirect: -14 of 31 prescribers responded (45,2 %) -10 prescribers authorized all the changes -10 of 41 recommendations were implemented by the patient (24,4 %) -73 medication reviews were completed: -41 recommendations were made to 32 patients		
Other studies (n=4)				
Fiß et al. 2013 (23) A prospective non-randomized implementation cohort study	• Patient data collection • Conducting the medication review • Counselling the patient • Contacting the GP	Indirect: - self-reported ADRs decreased non-significantly (McNemar, p = 0.564) - The proportion of patients taking PIM according to the Beers' criteria was reduced non-significantly (p = 0.07) - number of active substances taken was reduced from 8 to 7 - the proportions of patients using medication charts and compliance aids increased significantly (p < 0.001) - self-reported forgetfulness (p = 0.001), proportion of intermittent drug intake (p < 0.001) and the proportion of patients with potentially clinical relevant drug-drug interactions (p < 0.001) reduced		
Kassam et al. 2001 (11) A process description	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient	Indirect: - 559 DRPs were found in 145 patients; 39% actual and 60 % potential, 1% not labelled - average 3,9 DRPs per patient - The most frequent DRP categories were where patient		

	• Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	requires drug therapy or requires influenza or pneumococcal vaccination - pharmacists made 613 recommendations; 502 to patients (mostly recommending pneumococcal or influenza vaccines) and 247 to physicians - physicians accepted 72 % and patients 76 % of recommendations - 551 SOAP (subjective, objective, assessment, plan) notes were written and 346 follow-up interventions recorded (62% of identified DRPs) - in 80% of the situations pharmacist consulted directly patient - in follow-up 40 % of the DPRs were resolved, controlled or improved.		
Raynor et al. 2000 (9) Intervention study	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP	Indirect: - 441 DRPs were identified of which 55 % (n=241) required the provision of information or advice, 24 % (n=106) required consultation with the GP and 20% (n=80) required changes in the presentation of the medicines - the number of patients with one or more problems reduced from 94 % to 58 % (McNemar, $p < 0.001$) -the median number of regular prescribed medicines fell from 6 to 5 (Wilcoxon ranked pairs, $p < 0.001$) - the proportion of patients who		-the average cost per patient of oral prescription medication for 28 days fell from £51,12 to £44,55 (Wilcoxon, $p < 0.001$) - the support program resulted in projected savings of £52 per patient per year

		reported non-adherence fell from 38 % to 14 % (McNemar, $p < 0.001$)		
Twigg et al. 2015 (24) Intervention study	• Identification of the patients to medication review intervention • Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	Direct: - a significant reduction (mean 0.116 (95% CI, -0.217 to -0.014)) in the total number of falls - pain scores over the course of the evaluation period appeared to increase (non-significantly) Indirect: - pharmacists made 142 recommendations to prescribers centered on potentially inappropriate prescribing of NSAIDs, PPIs or duplication of therapy - adherence to medication improved significantly (0.513 (95% CI, 0.337 to 0.689) difference in scores)	-Quality of life improved significantly (mean change in score of 0.025 (95% CI, 0.007 to 0.042)	- cost of the intervention was estimated to be £98.72 per participant - cost per quality-adjusted life year estimates ranged from £11 885 to £32 466 depending on the assumptions made - based on the CEAC, at £20 000 per QALY, the probability of being cost-effective was 13.8%
III Clinical medication reviews				
RCTs (n=1)				
Bryant et al. 2011 (19)	• Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient	Indirect: - MAI significantly improved in the intervention group (at 6 months: 2.0 points; 95% confidence interval 1.32 to 2.68, $p < 0.001$) - 2,8 recommendations per patient in the intervention group - in the first 6 months, 38% of the pharmacists' recommendations were implemented and 12% partially implemented and in 12 months 46 % were implemented and 16 % partially implemented - 3,1 changes (intervention) vs.	- QoL: emotional role (13.4 unit difference, $p = 0.024$ and social functioning (7.7 unit difference, $p = 0.019$) significantly reduced in intervention group compared with the control	

		1,8 changes (control) per patient in the first 6 months - significantly more medicines started in the control group ($p < 0.0001$) - significantly more dosage reductions and medicines switches in the intervention group ($p = 0.037$)		
Other studies (n=6)				
Bryant et al. 2010a (15) Interview	• Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient		-Community pharmacists perceived that they were not mandated to undertake this role and it was not a legitimate role. They were concerned that they lacked the skills and confidence to provide this level of input.	
Bryant et al. 2010b (16) Interview	• Patient data collection • Interviewing the patient • Conducting the medication review • Counselling the patient • Contacting the GP • Following up the patient		-Two themes: patient outcomes (clinical vs. theoretical recommendations) and resource utilisation (time and funding) were balanced which determined the value. This led to a continuum between positive and negative responses.	
Castelino et al. 2010a (17) A retrospective analysis	• Patient data collection • Interviewing the patient • Conducting the medication review • Contacting the GP	Indirect: - the median cumulative patient MAI scores were significantly lower after the HMR (18.6 +/- 11.3 vs. 9.3 +/- 7.5), as interpreted from the pharmacist recommendations ($p < 0.001$)		
Castelino et al. 2010b (18) A retrospective analysis	• Patient data collection • Interviewing the patient • Conducting the medication review • Contacting the GP	Indirect: - significant reduction in the sum of total of DBI scores for all patients was observed following pharmacist recommendations during the HMR service (206.9 vs. 157,3, Wilcoxon signed-rank test, p <		

		0.001) - of the 372 patients, 148 (39,8 %) were prescribed one or more PIMs - pharmacists' recommendations led to a decrease in the use of PIMs, which were identified in 105 (29,2 %) patients of the 372 patients - ceasing the sedative or anticholinergic medication was the most frequently recommended action - pharmacists' recommendations during the HMR service, medications contributing to the DBI were identified in 51.6% (n = 192) of the patients.		
Freeman et al. 2012 (21) A retrospective analysis of medication reviews with two time periods	• Patient data collection			- 56% of the medication reviews from pre-integration phase and 6% from the post-integration phase were not billed which demonstrates a potential financial saving of AUS$ 17 374 during the post-integration phase - the time to complete the medication review process was significantly reduced from median of 56 days to 20 (p > 0.001) - in the post-integration phase more patients were seen within 2 and 4 weeks when compared to the pre-integration phase
Leikola et al. 2012 (22) A retrospective analysis	• Patient data collection • Interviewing the patient • Conducting the medication review	Indirect: - community pharmacists reported 785 potential DRPs (average of 6.5 per/patient)		

	• Contacting the GP	- the mean number of DRPs was higher for home-dwelling patients (7.2) than for the patients living in assisted-living setting (5.5) (p = 0.014) but similar in nature - The most common DRPs were inappropriate drug selection (17 % of DRPs) involving most often hypnotics and sedatives. Also, indications with no treatment were common (16%), particularly those associated with cardiovascular diseases and osteoporosis, the distribution of DRPs was similar in both groups - in 51% of DRPs (n=403), CMRs resulted in change of drug therapy; stopping a drug was the most common change - pharmacists made 649 recommendations, of which 55% (n=360) were accepted by physicians without revision		

ADR = Adverse drug reaction
CEAC = Cost-effectiveness acceptability curve
CMR = Comprehensive medication review
DBI = Drug Burden Index
DRP = Drug-related problem
GP = General practitioner
HMR = Home Medicines Review
HRQoL = Health-related quality of life
MAI = Medication Appropriateness Index
NSAID = Nonsteroidal anti-inflammatory drug
PIM = Potentially Inappropriate Medications
PPI = Proton pump inhibitor
QALY = Quality-adjusted life year
QoL = Quality of life
RCT = Randomized controlled trial
SOAP = Subjective, objective, assessment, plan